

## Factors Predicting the Efficacy of Adefovir Dipivoxil on Treatment-Naïve Chronic Hepatitis B Patients at 48 Weeks

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**Background/Aims:** To reveal possible factors predicting the effect of adefovir dipivoxil (ADV) treatment on chronic hepatitis B (CHB) and optimize the utilization of ADV. **Methods:** In total, 168 treatment-naïve CHB patients were enrolled, including 117 hepatitis B e antigen (HBeAg)-positive patients and 51 HBeAg-negative patients who met the inclusion criteria. All patients were treated with ADV 10 mg per day for 48 weeks. Multiple logistic regression analyses were used to investigate baseline factors, and responses at weeks 12 and 24 were analyzed as predictive values. **Results:** Multiple regression analyses showed that baseline HBeAg status and HBV DNA levels significantly affected the virological response (VR) ( $p < 0.05$ ), baseline ALT levels were an independent predictor of serological response (SR) ( $p < 0.05$ ) and the body mass index (BMI) may affect the biochemical response (BR) ( $p < 0.05$ ). There was a statistically significant difference in the VR and SR between patients with a primary nonresponse (PNR) at week 12 and those with a VR at week 12 ( $p < 0.01$ ). Additionally, the VR was significantly different between patients with HBV DNA lower than  $10^3$  copies/mL at week 24 and those with greater than  $10^3$  copies/mL ( $p < 0.01$ ). **Conclusions:** Patients with negative HBeAg, lower HBV DNA levels and higher ALT values at baseline are more suitable for ADV treatment, whereas patients with lower BMIs may be more amenable to ALT normalization. Adjustments for treatment strategy should be considered if PNR at week 12 or HBV DNA  $\geq 10^3$  copies/mL at week 24 is observed. (*Gut Liver* 2011;5:478-485)

**Key Words:** Adefovir dipivoxil; Antiviral therapy; Chronic hepatitis B; Predictive factors

## INTRODUCTION

In recent years, multiple evidences confirmed that antiviral treatment with nucleoside analogues of chronic hepatitis B (CHB) could inhibit viral replication, improve liver function, reduce the incidence of decompensated liver diseases, including cirrhosis and liver cancer, and thus improve the prognosis of diseases.<sup>1</sup> With progressive scope in clinical application and research in this field, philosophy of antiviral therapy has transformed from simple application with a personal preference to optimization therapy, including determination of the most favorable target population, option of initial drug, adjustment followed by response, management for drug resistance, combination or sequential treatment, etc.<sup>2-4</sup>

Among 4 available nucleoside analogues in China,<sup>5</sup> adefovir dipivoxil (ADV) has been widely used for the treatment of CHB due to its abilities to reduce the viral load, normalize the liver function, improve the liver histology, and show a few side effects and due to its cost effectiveness and low occurrence rate of drug-resistance after long-term use.<sup>6,7</sup> However, different responses of ADV on CHB patients were found in clinical practice, and some of them showed unsatisfactory effects such as primary nonresponse (PNR) or partial response. The efficacy of drugs was affected both by the virus and host factors. Therefore, it is very important to analyze predictive factors for the effect of ADV so as to optimize its effects including screening more qualified patients at beginning of treatment, adjusting treatment strategy according to some useful valuable indicators during the treatment. However, as clinical data about predictive factors during the treatment for the efficacy of ADV are mainly from patients with LAM-resistance, primary data of ADV monotherapy

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py in naïve CHB patients are rare, and the effect-related factors remain still unclear.

In this study, a total of 168 naïve CHB patients who received ADV monotherapy for 48 weeks, were enrolled and a preliminary investigation on possible predictive factors for the effect of ADV was carried out to provide the grounds for optimization therapy.

## MATERIALS AND METHODS

### 1. Patients and study design

This study was performed by retrospective chart review. Patients who visited the outpatient clinic of West China Hospital of Sichuan University from March 2007 to June 2008 and met the inclusion criteria were enrolled in this study. The inclusion criteria were as follows: positive for hepatitis B surface antigen (HBsAg) for at least 6 months and without history of antiviral therapy with nucleoside analogues; alanine aminotransferase (ALT) levels between 2 to 10 times the upper normal levels; HBV DNA levels  $\geq 10^5$  copies/mL for hepatitis B e antigen (HBeAg)-positive patients and  $\geq 10^4$  copies/mL for HBeAg-negative patients. Patients were excluded if coinfecting with HIV and other hepatitis viruses, nonalcoholic fatty liver disease, alcoholic liver disease, post-hepatic cirrhosis and hepatocellular carcinoma. The diagnosis of fatty liver depends on characteristic rise of liver enzymes including  $\gamma$ -glutamyltransferase, change of ultrasound Doppler and other underlying diseases with metabolic disorder.<sup>8</sup> Diagnosis of alcoholic liver disease depends on alcohol consumption, drinking life and special imaging examination including ultrasound Doppler and/or computed tomography (CT).<sup>9</sup> Liver cirrhosis can be confirmed through invasive and noninvasive techniques including liver stiffness measurement, special imaging examination and liver biopsy.<sup>10</sup> Hepatocellular carcinoma also can be diagnosed by elevated A fetal protein and characteristic imaging manifestation including CT and/or magnetic resonance imaging (MRI).<sup>11</sup>

All patients were given ADV 10 mg daily as antiviral treatment for at least 48 weeks (mean duration of treatment was 52 weeks). Patients who discontinued medication before 48 weeks were not included in this study. During the treatment period, patients were not given any other antiviral drugs and medicines for liver function protection.

### 2. Serum assays

Analyses of liver and renal functions, which included serum levels of total bilirubin (TB), ALT, albumin, blood urea nitrogen (BUN), creatine, and serum electrolyte, were performed at baseline, and at weeks 12, 24, 36, and 48 of ADV treatment, using the Automatic Biochemistry analyzer (Olympus AU5400; Olympus Co., Tokyo, Japan). Statuses of HBsAg, HBeAg, and antibodies to HBeAg (anti-HBe) were measured by a microparticle enzyme-linked immunosorbent assay at baseline, and

weeks 24 and 48. Serum HBV DNA was quantified by real-time polymerase chain reaction (LightCycler480; Roche Diagnostics, Mannheim, Germany) at baseline and weeks 12, 24, 36, and 48, with a linear range between  $1 \times 10^3$  and  $5 \times 10^7$  copies/mL (Da An Gene Co., Ltd. of Sun Yat-Sen University, Guangzhou, China). ADV-associated mutations were assessed via direct sequencing if virological breakthrough occurred during the treatment. All assays were performed in microbiological laboratories in West China Hospital of Sichuan University.

### 3. Definition and evaluation of efficacy

Virological response (VR) was defined as a reduction of HBV DNA levels to less than detection level ( $< 10^3$  copies/mL). Biochemical response (BR) was defined as a normalization of ALT levels. Serological response (SR) was defined as disappearance of HBeAg with or without the appearance of HBeAb. PNR was defined as a decline less than 1 log of HBV DNA levels at week 12 of the treatment according to EASL Clinical Practice Guidelines of 2009.<sup>12</sup> Non PNR was defined in comparison with PNR as a decline more than 1 log of HBV DNA levels at week 12 of the treatment. Virological breakthrough was defined as a  $> 1$  log copies/mL increase in serum HBV DNA compared to the on-treatment nadir that was confirmed in 2 consecutive tests. Drug resistance (DR) was defined as the emergence of virological breakthrough and presence of drug resistance mutations.

The antiviral efficacy of ADV was assessed at weeks 12, 24, and 48 during treatment. Rates of VR, BR, SR, PNR, and DR were assessed at the above mentioned time points respectively. Baseline factors including age, gender, body mass index (BMI), HBeAg status, ALT, and DNA levels were analyzed for their influence on the effect of ADV treatment. PNR at week 12 and HBV DNA levels at week 24 were analyzed as predictive factors during the treatment.

### 4. Statistical analysis

Quantitative data were presented as the mean  $\pm$  standard deviation, categorical data were presented as counts and percentages, and HBV DNA levels were presented as log transformation. Data were analyzed using the SPSS software package version 13.0 (SPSS Inc., Chicago, IL, USA). Pearson chi-square or Fisher exact tests were used for categorical variables. Logistic regression analysis was used to investigate the baseline predictors for the response of treatment. In all cases, tests of significance were two-tailed, and significance was defined for  $p < 0.05$ .

## RESULTS

### 1. General information

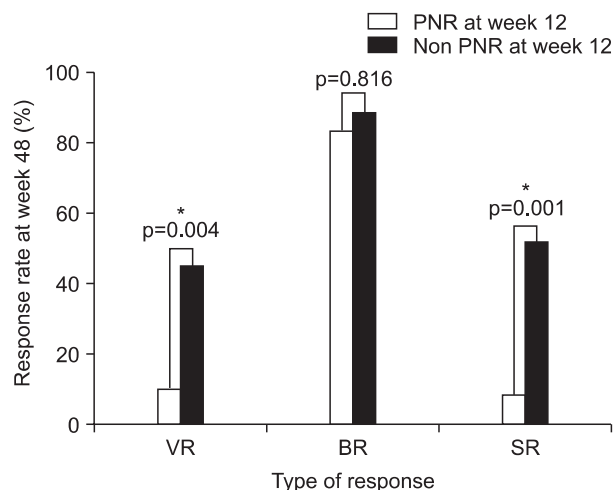
A total of 168 patients were included, consisted of 119 (70.83%) males and 49 (29.17%) females, with ages ranging from 18 to 45 years (mean,  $29.92 \pm 6.78$  years) and BMI ranging from 17.22 to 27.34 (mean,  $21.64 \pm 1.83$ ). Baseline data were as

follows: for 117 HBeAg-positive patients, the median level of HBV DNA was  $5.00 \times 10^7$  copies/mL and the mean level of ALT was  $197.58 \pm 110.93$  IU/mL; for 51 HBeAg-negative patients, the median level of HBV DNA was  $1.76 \times 10^6$  copies/mL and the mean level of ALT was  $171.23 \pm 125.83$  IU/mL.

## 2. Virological effect

Of the 117 HBeAg-positive patients, reduction of HBV DNA level was  $2.13 \pm 1.31$ ,  $2.79 \pm 1.23$ , and  $3.22 \pm 1.16$  lg copies/mL at weeks 12, 24, and 48 respectively compared with that of the baseline; and VR was observed in 7.69% (9/117), 17.95% (21/117), and 28.21% (33/117) of patients at weeks 12, 24, and 48, respectively.

Of the 51 HBeAg-negative patients, reduction of HBV DNA level was  $2.32 \pm 1.17$ ,  $2.81 \pm 1.04$ , and  $3.00 \pm 1.12$  lg copies/mL at weeks 12, 24, and 48 respectively compared with that of the baseline; and VR was observed in 17.65% (9/51), 52.94% (27/51), and 62.75% (32/51) of patients at weeks 12, 24, and 48, respectively.



**Fig. 1.** Comparison of responses between patients with primary non-response (PNR) at week 12 and patients with nonPNR at week 12. BR, biochemical response; SR, serological response; VR, virological response. \* $p < 0.05$ .

## 3. Biochemical effect

Of the 117 HBeAg-positive patients, ALT normalization was achieved in 42.74% (50/117), 67.52% (79/117), and 87.18% (102/117) at weeks 12, 24, and 48, respectively.

Of the 51 HBeAg-negative patients, ALT normalization was achieved in 64.71% (33/51), 74.51% (38/51), and 88.24% (45/51) at weeks 12, 24, and 48, respectively.

## 4. Serological effect

Of the 117 HBeAg-positive patients, the disappearance of HBeAg was observed in 10.26% (12/117) and 43.59% (51/117) of patients at weeks 24 and 48, respectively. An HBeAg/anti-HBe seroconversion was achieved in 5.13% (6/117) and 15.38% (18/117) of patients at weeks 24 and 48, respectively.

## 5. PNR

For HBeAg-positive patients at week 12, the rate of PNR was 20.51% (24/117). And for HBeAg-negative patients at week 12, the rate of PNR was 11.76% (6/51) (Fig. 1).

## 6. Resistance and side effects

By week 48, no virus breakthrough occurred in all patients. Overall, ADV demonstrated a good safety profile. All levels of serum electrolytes were normal. Mild adverse reactions were observed only in 5 (2.98%) patients, including 4 patients with a transient mild increase of BUN. The patients were monitored closely and no other drugs were given, and BUN value returned to normal level gradually. Another patient suffered from insomnia symptom, which disappeared after symptomatic treatment.

## 7. Logistic regression analysis of baseline impact factors for antiviral effect of ADV

If VR at week 48 was regarded as outcome variable, the results of multiple logistic regression analyses of factors at baseline showed that baseline HBeAg status and baseline HBV DNA level were independent factors of week 48 VR ( $p < 0.05$ ). Values of odds ratio (OR) showed that it was easier to achieve undetectable HBV DNA level at week 48 in patients with negative-HBeAg and lower HBV DNA levels compared with patients with

**Table 1.** Analyses with VR at Week 48 as the Outcome Variable

Baseline factor	$\beta$	SE	Df	p-value	OR	95% CI
Age	0.061	0.037	1	0.123	1.062	0.986–1.153
Gender	-0.868	0.465	1	0.075	0.420	0.153–1.062
BMI	-0.234	0.139	1	0.094	0.791	0.597–1.041
HBeAg status	1.118	0.461	1	0.021	3.059	1.130–7.596
HBV DNA	0.111	0.102	1	0.031	1.697	1.015–3.256
ALT	0.001	0.002	1	0.673	1.001	0.997–1.005

VR, virological response;  $\beta$ , coefficient; SE, standard error; Df, degree of freedom; OR, odds ratio; CI, confidence interval; BMI, body mass index; HBeAg, hepatitis B e antigen; DNA, deoxyribonucleic acid; ALT, alanine aminotransferase.

**Table 2.** Analyses with BR at Week 48 as Outcome Variable

Baseline factor	$\beta$	SE	Df	p-value	OR	95% CI
Age	-0.027	0.042	1	0.625	0.973	0.869–1.083
Gender	-0.599	0.633	1	0.420	0.549	0.126–2.299
BMI	0.407	0.164	1	0.045	1.503	1.006–2.243
HBeAg status	-0.681	0.118	1	0.343	0.506	0.112–1.997
HBV DNA	0.000	0.533	1	0.286	0.591	0.280–1.771
ALT	-0.002	0.003	1	0.577	0.998	0.992–1.004

BR, biochemical response;  $\beta$ , coefficient; SE, standard error; Df, degrees of freedom; OR, odds ratio; CI, confidence interval; BMI, body mass index; HBeAg, hepatitis B e antigen; DNA, deoxyribonucleic acid; ALT, alanine aminotransferase.

**Table 3.** Analyses with SR at Week 48 as Outcome Variable

Baseline factor	$\beta$	SE	Df	p-value	OR	95% CI
Age	0.013	0.034	1	0.772	1.013	0.918–1.055
Gender	-0.620	0.447	1	0.262	0.538	0.289–1.697
BMI	-0.017	0.131	1	0.908	0.983	0.724–1.202
HBV DNA	0.000	0.098	1	0.389	0.762	0.572–1.408
ALT	-0.006	0.002	1	0.015	0.994	0.991–0.999

SR, serological response;  $\beta$ , coefficient; SE, standard error; Df, degrees of freedom; OR, odds ratio; CI, confidence interval; BMI, body mass index; DNA, deoxyribonucleic acid; ALT, alanine aminotransferase.

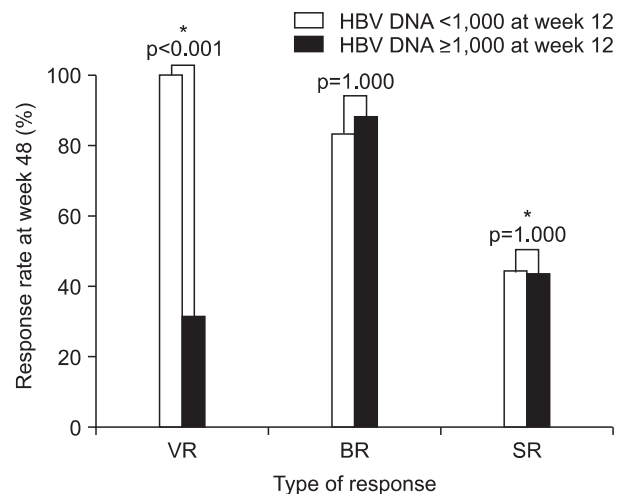
positive-HBeAg and higher HBV DNA levels at baseline (Table 1).

If BR at week 48 was regarded as outcome variable, the results of multiple logistic regression analyses of factors at baseline showed that BMI was an independent factor of week 48 BR ( $p < 0.05$ ). Values of OR showed that it was easier to achieve the normalization of ALT at week 48 in patients with lower BMI compared with patients with higher BMI at baseline. The results also showed that both baseline HBeAg status and baseline HBV DNA level were not impact factors for BR (Table 2).

When SR at week 48 was regarded as outcome variable, the results of multiple logistic regression analyses of factors at baseline showed that baseline ALT level was an independent factors of week 48 SR ( $p < 0.05$ ). Values of OR showed that it was easier to achieve the HBeAg disappearance at week 48 in patients with higher ALT levels compared with patients with lower ALT level at baseline. The results also show that both baseline HBeAg status and baseline HBV DNA level were not impact factors on SR (Table 3).

#### 8. The PNR of week 12 as predictive factor during treatment for efficacy of week 48

For 30 patients with PNR at week 12, the rates of VR, BR, and SR at week 48 were 10% (3/30), 83.33% (25/30), and 8.33% (2/24), respectively. But for the other 138 patients with non PNR at week 12, the rates of VR, BR, and SR at week 48 were 44.93% (62/138), 88.41% (122/138), and 52.69% (49/93), respectively. The difference in VR and SR between the 2 groups was statistical significant ( $p = 0.004$ ,  $p = 0.001$ ), but similar in BR ( $p = 0.816$ ).

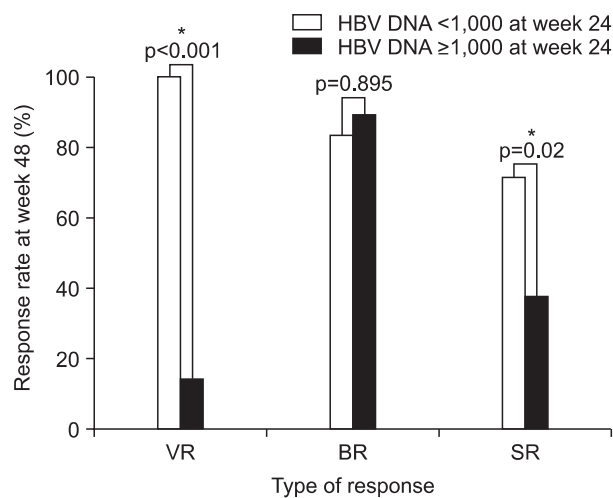


**Fig. 2.** Comparison of responses between patients with HBV DNA <10<sup>3</sup> copies/mL and patients with HBV DNA ≥10<sup>3</sup> copies/mL at week 12.

HBV, hepatitis B virus; VR, virological response; BR, biochemical response; SR, serological response. \* $p < 0.05$ .

#### 9. The rate of HBV DNA <10<sup>3</sup> copies/mL at weeks 12 and 24 as predictive factor during treatment for efficacy of week 48

For 18 patients with HBV DNA <10<sup>3</sup> copies/mL at week 12, the rates of VR, BR, and SR at week 48 were 100% (18/18), 83.33% (15/18), and 44.44% (4/9), respectively. But for the other 150 patients with HBV DNA ≥10<sup>3</sup> copies/mL at week 12, the rates of VR, BR, and SR at week 48 were 31.33% (47/150),



**Fig. 3.** Comparison of responses between patients with HBV DNA <10<sup>3</sup> copies/mL and patients with HBV DNA ≥10<sup>3</sup> copies/mL at week 24.

HBV, hepatitis B virus; VR, virological response; BR, biochemical response; SR, serological response. \*p<0.05.

88% (132/150), and 43.52% (47/108), respectively. Between the 2 groups the difference in VR was statistically significant (p<0.001), but not statistically significant in BR and SR (p=1.000) (Fig. 2).

For 48 patients with HBV DNA <10<sup>3</sup> copies/mL at week 24, the rates of VR, BR, and SR at week 48 were 100% (48/48), 83.33% (40/48), and 71.44% (15/21), respectively. But for the other 120 patients with HBV DNA ≥10<sup>3</sup> copies/mL at week 24, the rates of VR, BR, and SR at week 48 were 14.17% (17/120), 89.17% (107/120), and 37.5% (36/96), respectively. The differences in both VR and SR between the 2 groups were statistically significant (p<0.001, p=0.02), but were not statistically significant in BR (p=0.895) (Fig. 3).

## DISCUSSION

The importance of optimization therapy of nucleoside analogues relies in its long-term treatment course and inevitable resistance occurrence. It is widely debated on how to screen patients who are the most qualified target population for certain drugs. During the therapy, efficacy predictions are usually performed to achieve the best effect, the lowest resistance occurrence and the highest effect-cost ratio. In recent years, optimization therapy of nucleoside analogues focused on the issues of baseline situation, considering early response and application of roadmaps.<sup>13</sup>

Due to its antiviral effect, lower drug-resistance, affordable price and no cross-resistance with other nucleoside analogues, ADV is still widely used in naïve CHB patients in certain countries including China and Asia. Although ADV was no longer included in 2009 EASL and AASLD guidelines as choice of first-line antiviral therapy,<sup>14</sup> its usage is estimated to continue in

many countries including China, as tenofovir will not be available in the next several years in these countries and it is much cheaper than Entecavir. Therefore research on predictive factors of antiviral efficacy of ADV is still important and would provide us better evidence for optimization therapy.

In this study, 168 cases of CHB patients who received at least 48 weeks' ADV treatment were included. The rates of VR, BR, and SR of 117 patients with positive HBeAg were 28.21%, 87.18%, and 43.59% after 48 weeks of treatment, respectively. The rates of VR and BR of 51 patients with negative HBeAg were 62.75% and 88.24%, respectively. These results suggest that the VR in HBeAg-negative patients were obviously higher than HBeAg-positive patients, but similar in BR. The results were similar and in accordance with other published data,<sup>15,16</sup> but extent of virus reduction and VR rate were not as impressive as previously reported.<sup>17-19</sup> The possible reason may be due to the high baseline of HBV-DNA levels, with 5.00×10<sup>7</sup> copies/mL median levels of HBV DNA. At the same time, virological breakthrough did not occur in patients with 48 weeks' therapy, ADV was well tolerated in all patients, and rate of adverse reaction was only 2.98%.

The present study investigated several baseline host and viral factors that may influence the antiviral efficacy, including age, gender, BMI, baseline HBeAg status, baseline HBV DNA and ALT levels. The results of multiple regression statistical analyses show that both the patient's age and gender had no impact on the VR, BR, and SR. With regard to BMI, it has been reported that sustained response of indinavir and saquinavir was related to weight in AIDS studies.<sup>20</sup> However, it has not been confirmed that the body weights were associated with VR in hepatitis C or hepatitis B.<sup>21</sup> In this study, the relationship between VR, SR, and BMI was also not confirmed. It means that higher BMI didn't show less effective viral suppression or not. Yet, it seems that BMI may influence BR, and the clinical significance of this conclusion is still worthy to be confirmed by further studies.

The results suggest that baseline HBeAg status and HBV DNA level significantly affected VR; especially higher VR was observed in patients with HBeAg-negative and lower HBV DNA at baseline. These results were similar to several previous reports,<sup>22,23</sup> and confirmed again that the curative effect of HBeAg-negative patients with lower baseline HBV DNA is superior to the effect of HBeAg-positive patients with higher HBV DNA. However, contradictory to other reports,<sup>19</sup> results of this study suggest that baseline ALT levels couldn't influence VR at week 48. The possible reason may be related to a close and little range of ALT levels and a small dispersion of patients in this group. The results showed that baseline HBeAg status, baseline HBV DNA and ALT levels had no effect on BR. The results of influencing factors analysis of SR showed that the occurrence of E-antigen disappearance or seroconversion was not significantly correlated with baseline HBV DNA, which was different with data published by Tseng *et al.*<sup>24</sup> However, the results



show a correlation between baseline ALT levels and SR. Patients with higher ALT levels at baseline achieved disappearance or seroconversion of HBeAg easier. A possible interpretation is that higher baseline ALT levels suggest a strong immune response, which facilitates the reconstruction of a specific immune response against HBV, thereby inhibiting the expression of HBeAg and promoting anti-HBe production. Yet, it is worth mentioning that as the observation period of this study lasted for only 48 weeks, the statistical conclusions of this study are limited and a long-term follow-up is needed.

Many studies suggest that genotype only affects the response of interferon therapy, but do not play a role in nucleoside analogues.<sup>25-27</sup> At the same time, the genotype determination in our country has not yet been widely used in clinical practice, such as in this study the correlation between the genotype and antiviral efficacy was not analyzed.

In this study, the predictive value of PNR at week 12 on effect of 48 weeks' therapy was analyzed. The results showed that the VR at week 48 were 10% and 44.3% respectively for patients with PNR and with nonPNR at week 12, and the difference in VR was statistically significant. At the same time, the difference in SR was also significant (8.33% vs. 52.69%). These results suggest that only 10% of patients with PNR at week 12 acquired VR at week 48, and only 8.33% acquired SR. Therefore, if PNR is observed at week 12, treatment strategies should be adjusted, including adding-on or switching to other agents. This point of view is similar to that of Hass *et al.*<sup>28</sup>

On the other hand, this study also discusses the predictive value of HBV DNA  $<10^3$  copies/mL at weeks 12 and 24 for VR, BR, and SR of week 48. The results show that the difference in 48 weeks' BR and SR was not statistically significant between patients with HBV DNA  $<10^3$  copies/mL at week 12 and those HBV DNA  $\geq 10^3$  copies/mL. However, a significant difference of 100% and 31.33% respectively was seen in VR. If the analysis was performed at week 24, the VR of the 2 groups were 100% and 14.17%, respectively, while difference in SR was also significant (71.44% vs. 37.5%). It can be seen that HBV DNA  $<10^3$  copies/mL at weeks 12 and 24 is a strong predictor of response, and is especially important for predicting VR at week 48. These results are also similar to other published reports.<sup>29,30</sup> Yet, which time point has a higher predictive value, week 12 or week 24? The results of this study suggest that 31.33% of patients with HBV DNA  $\geq 10^3$  copies/mL at week 12 could still achieve VR at week 48, but if HBV DNA was still  $\geq 10^3$  copies/mL at week 24, only 14.17% patients were able to achieve VR at week 48, with a significant difference in SR between HBV DNA  $\geq 10^3$  copies/mL and HBV DNA  $<10^3$  copies/mL at week 24. So the results of this study suggest that treatment strategies should be assessed and adjusted at week 24 instead of week 12 according to whether HBV DNA level had reduced to lower than  $10^3$  copies/mL. Strategies such as adding-on or switching to other agents can be considered.

Of the 168 cases in this study, no virological breakthrough was observed. However, the observation period lasted only 48 weeks. With the extension of treatment course, the occurrence of drug-resistance may increase gradually. Therefore, it is necessary to monitor the occurrence of drug resistance with ongoing treatment. At the same time, even though the incidence of adverse reactions of ADV in the study was low and therapy could be applied also for children,<sup>31</sup> it is necessary to monitor the kidney function closely,<sup>32</sup> particularly in kidney transplant patients<sup>33</sup> due to its kidney damage potential. Additionally, the incidence of hypolipidemia with low phosphate should be considered.<sup>34</sup>

In summary, our results suggest the following conclusions: ADV has efficacy in CHB patients, with a good safety profile and no resistance at week 48. In particular, patients with negative HBeAg, lower HBV DNA level and higher ALT values at baseline would be more suitable for ADV therapy, while patients with lower BMI may have some advantages on ALT normalization. On the other hand, during the course of treatment, it is crucial to focus on the response of weeks 12 and 24. In case a PNR is seen at week 12 or  $>10^3$  copies/mL at week 24, alteration or adjustment of treatment strategy should be considered.

The primary limitations of this study lie in the relatively short observation time period and the small number of patients. In addition, our HBV DNA assay has limited dynamic range only between  $1 \times 10^3$  and  $5 \times 10^7$  copies/mL. This limits accurate assessment of antiviral efficacy of adefovir in this study. However, the results of this study suggest some clues and indicators with clinical value in 48 weeks' observation period. Further studies continuing treatment for longer terms with more improved HBV DNA assay allowing wider detection limits are warranted.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Li-Chun Wang and En-Qiang Chen contributed equally to this paper for analyzing the data and writing the paper. Hong Tang proposed the study, and all authors contributed to the interpretation of the study and to further drafts. Hong Tang is the guarantor.

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